REMARKS

Applicants have carefully studied the Supplemental Office Action mailed July 23, 2010, which issued in connection with the above-identified patent application. Applicants understand that the Supplemental Office Action issued on July 23, 2010 replaces the Office Action issued on May 11, 2010.

The present response is intended to be fully responsive to all points raised by the Examiner in the July 23, 2010 Supplemental Office Action and is believed to place the claims in condition for allowance. Favorable consideration and allowance of the present claims are respectfully requested.

I. Telephone Interviews with Examiner Boesen

Applicants gratefully acknowledge the courtesy shown by Examiner Agnieszka Boesen during telephonic interviews with Applicants' representative, Irina Vainberg, on May 12, 2010 and May 20, 2010.

The Interview Summaries mailed on May 17, 2010 and May 25, 2010 are believed to accurately reflect the substance of the interviews. As indicated in the Interview Summary mailed on May 25, 2010, the Examiner vacated the Office Action dated May 11, 2010 in light of the arguments presented at both interviews.

II. Pending Claims

Claims 1, 3, 4, 9-13, 15-20, 22, 23, 28-31, 33-37, 40, 45, 46, 51-53 and 56 were pending in this application. Claims 11-13, 15-19, 29-31, 33-37, and 40 have been withdrawn from consideration as directed to non-elected invention, and Claims 54 and 55 were previously canceled without prejudice or disclaimer.

III. Anticipation Rejections

Claim 1 has been rejected under 35 U.S.C. § 102(a) as being anticipated by Sigurdsson et al. (American Journal of Immunology, 2002, Vol. 161, p. 13-17) (hereafter, "Sigurdsson"), and has been rejected under 35 U.S.C. § 102(b) as being anticipated by Williamson et al. (PNAS, 1996, Vol. 93, pp. 7279-7282) (hereafter, "Williamson"), or by Prusiner et al. (U.S. Patent No. 6,290,954) (hereafter, "Prusiner").

Applicants respectfully traverse the rejections.

Claim 1 specifies a composition comprising a non-infectious, non-pathogenic mammalian prion protein, wherein the composition elicits a primarily Th-2-type immune response not associated with a primarily Th-1-type CTL response, when introduced to a mammalian mucosal immune system, and requires the composition to be suitable for mucosal administration. None of the cited references teach or suggest a composition having these claimed functional properties, as discussed in detail, below.

The Examiner alleges that Sigurdsson discloses a composition that is suitable for mucosal administration and induces a primarily Th2-type immune response. Applicants respectfully disagree. Sigurdsson's compositions contain Complete Freund's Adjuvant (CFA) or Incomplete Freund's Adjuvant (IFA). CFA and IFA are water-in-oil emulsions, with CFA additionally containing heat-killed mycobacteria or its components (e.g., cell wall), which are used as injectable adjuvants. Applicants respectfully submit that CFA and IFA are not suitable for mucosal administration, because they would not function properly as adjuvants in mucosal sites. When injected, e.g., subcutaneously or intraperitoneally, the adjuvant activity of CFA and IFA is a result of sustained release of antigen from the oily deposit at the site of injection (reviewed by Scheibner et al. "Vaccines" Nexus (2000) 8(1) (available at www.whale.to/vaccine/adjuvants.html and attached as Exhibit H). At mucosal sites, e.g., the gut, however, this sustained release would not be possible, since the oil, and any antigen associated with it, would simply be digested, like any other food, thereby preventing sustained release of the antigen. Further, the hyper-viscous oil of

CFA and IFA would prevent the emulsion from crossing mucosal barriers, thereby preventing the immune system's access to the antigen.

Applicants respectfully submit that it is well-known in the art that CFA and IFA are not suitable for mucosal administration, as required by claim 1, and are only used for parenteral administration, and more particularly are intended for use in injectable compositions. This is evidenced, for example, in "Guidelines for the Research Use of Adjuvants," published by the National Institutes of Health, available online at http://oacu.od.nih.gov/ARAC/documents/Adjuvants.pdf, and attached as Exhibit A. In the Guidelines, the NIH states, "CFA, a water-in-oil emulsion containing heat-killed mycobacteria or mycobacterial cell wall components, is an effective means of potentiating cellular and humoral antibody response to **injected** immunogens." See, Exhibit A, page 1, third paragraph (emphasis added). Applicants also direct the Examiner's attention to Table 1 on page 3 of Exhibit A, which summarizes the different routes of administration of CFA, which include subcutaneous, intradermal, interaperitoneal, footpad, and intramuscular (i.e., all parenteral routes and no mucosal routes of administration).

Examples of other published guidelines which show that CFA is only intended for injection include those available from the University of Minnesota's website, in "Guidelines for Immunization of Research Animals," published online at http://www.ahc.umn.edu/rar/immun.html and attached as Exhibit B, which state that, "[i]njections containing Freund's complete adjuvant should be given subcutaneous (SQ), rather than intradermal (ID), intramuscular (IM), intravenous (IV) or intraperitoneal (IP)." See section entitled "Route of Administration." See also, Exhibit C, "Use of Complete Freund's Adjuvant in Laboratory Animals," guidelines published by the University of Pennsylvania and available online at the website, http://www.upenn.edu/regulatoryaffairs/Pdf/3UseOfCompleteFreundAdjuvant.pdf.

Applicants further point the Examiner to U.S. Patent Application Publication No. 2006/0165722 by De Magistris, which discloses that while systemic adjuvants such as CFA are suitable for systemic administration, mucosal vaccines require specific adjuvants, and adjuvants that

work for systemic immunization "generally are not effective for mucosal immunization" (see, paragraphs [0007 – 0008]).

Even, assuming *arguendo*, that these adjuvants could be suitable for mucosal administration, CFA-containing compositions, in fact, are known to have an opposite functional property as the claimed composition, since, as shown by Gottwein et al. (2001) J. Infect. Dis.; 184:308-314; (Exhibit D), CFA-containing compositions are known to induce a primarily Th-1-type CTL immune response, and IFA-containing compositions, especially those containing non-infectious, non-pathogenic antigens, would be expected to induce tolerance. See, e.g., Exhibit E, Heeger et al. (2000) J. Immunol.; 164;5771-5781. Since Claim 1 requires the composition not only to be suitable for mucosal administration, but also to induce a primarily Th2-type mucosal immune response, Sigurdsson's CFA and IFA-containing compositions fail to anticipate the claimed compositions for this additional reason.

The Examiner alleges that Williamson and Prusiner both disclose compositions comprising isolated, non-infectious, non-pathogenic prion protein. Applicants respectfully disagree. In contrast to the Examiner's assertion, Williamson and Prusiner only disclose compositions comprising **pathogenic**, **infectious** prion rods (mouse (mo) and/or Syrian hamster (SHa) PrP 27-30). As described in Caughey et al., (1991); Biochemistry; 30:7672-7680; attached as Exhibit F, PrP 27-30 is a protease-resistant form of normal prion protein that has been identified as the major component of brain fraction enriched for ***scrapie infectivity***. See, Exhibit F, at Abstract (emphasis added). Williamson and Prusiner isolated PrP 27-30 from the brains of mice or Syrian hamsters that were clinically ill with scrapie (prion disease). See, e.g., Williamson at page 7279, right column, lines 29-42, and Prusiner at column 29, lines 19-23, and lines 39-50. Further, Williamson discloses that, "PrP 27-30 polymerizes into rod-shaped particles with the tinctorial properties of amyloid but that can be dispersed into detergent-lipid-protein complexes (DLPC) with *retention of scrapie* ***infectivity***." See, Williamson, page 7281, left column, lines 48-51. Thus, Applicants respectfully submit that Williamson and Prusiner fail to disclose a composition containing a non-infectious, non-pathogenic prion protein, as required by Claim 1.

Moreover, Williamson and Prusiner both disclose compositions containing CFA and/or IFA, which they inject intraperitoneally. See, Williamson, page 7279, right column, line 43, to page 7280, left column, line 1; Prusiner, column 29, lines 51-61. As discussed above, compositions containing CFA or IFA are not suitable for mucosal immunization, as required by Claim 1, and thus, Williamson and Prusiner fail to anticipate the claim.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil. Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP §2131.

In light of the above arguments and standards, applicants submit that Claim 1 is patentable over Sigurdsson, Williamson and Prusiner. Applicants respectfully request that the anticipation rejection of Claim 1 be withdrawn.

IV. Obviousness Rejections

Claims 3, 4, 9, 10, 53 and 56, which all depend from Claim 1, are rejected under 35 U.S.C. § 103(a) as being obvious over Sigurdsson, or in alternative with Prusiner, or in alternative with Williamson, in view of one or more of the following secondary references: U.S. Patent 5,733,760 by Lu et al. ("Lu"), Chabalgoity et al. (Vaccine, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005) ("Chabalgoity"), U.S. Patent Application Publication No. 2002/0194635[1] by Dunne et al. ("Dunne"), Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285) ("Benkirane"), Clements et al. (US Patent No. 6,440,423) ("Clements"), and Kleanthous et al. (US Patent No. 6,585,975) ("Kleanthous").

Claim 20 and its dependent Claims 22, 23, 28, 45, 46, 51, 52 and 53 have been rejected under 35 U.S.C. § 103(a) as being obvious over Sigurdsson, or in alternative with Prusiner, or in alternative with Williamson, in view of one or more of the following secondary references: U.S.

[1] Applicants note that the publication number of Dunne et al. was incorrectly cited in the Office Action as 2002/0194634. Applicants thank the Examiner for providing the correct number following a telephone discussion.

Patent 5,733,760 by Lu et al. ("Lu"), Chabalgoity et al. (Vaccine, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005) ("Chabalgoity"), Grones and Turna (Biochemical and Biophysical Research Communications, 1995, Vol. 206, pp. 942-947) ("Grones"), U.S. Patent Application Publication No. 2002/0194635 by Dunne et al. ("Dunne"), and Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285) ("Benkirane").

The rejections are respectfully traversed.

Sigurdsson discloses compositions containing CFA or IFA. As described in detail in the previous section, CFA and IFA are not suitable for mucosal administration. Moreover, the skilled artisan is not taught by Sigurdsson to substitute another adjuvant, e.g., one that is suitable for mucosal administration, for CFA or IFA, since, at the time of the publication of Sigurdsson, the understanding in the field was that it was extremely difficult to break tolerance (e.g., induce a CD4 T cell-mediated immune response) to antigens regarded by the immune system as self antigens, such as e.g., endogenous prion proteins. See, e.g., Sigurdsson, which states, "[n]one of the prionoses currently have an effective treatment," and, "we sought to determine how overcoming the *natural immunological tolerance* to PrP by active immunization would influence progression of the disease." Sigurdsson at Abstract, and page 13, right column, lines 11-14 (emphasis added).

In order to try to overcome immunological tolerance, Sigurdsson included a very strong adjuvant, CFA, in his immunizing composition.[2] However, even when CFA was used, Sigurdsson's compositions failed to induce a protective immune response, since none of his treatment paradigms prevented prion disease. See, e.g., Sigurdsson, page 15, right column, lines 18-22. Since, even though they were administered subcutaneously with a strong adjuvant (CFA), Sigurdsson's compositions did not induce an immune response that was sufficient to treat prionoses, the skilled artisan would have had no reason to expect that Sigurdsson's composition would work better if administered mucosally. In fact, the understanding at that time, as Applicants have argued

[2] Subsequent booster compositions contained IFA rather than CFA, in accordance with NIH approved protocols, however IFA-containing compositions were only used as boosters, and would not be expected to induce an immune response without the initial immunization with a CFA-containing composition (i.e., an IFA-containing composition would not be expected to be capable of inducing a cellular immune response (e.g. Th2 response) on its own.) See, e.g., Exhibit E.

previously, and as discussed in detail in Czerkinsky et al. (1999) Mucosal Immunity and Tolerance: Relevance to Vaccine Development; Immunological Reviews; 170:197-222) (Exhibit G), was that it is extremely difficult to break tolerance to self antigens mucosally. For example, Czerkinsky states, "[i]mmunologic unresponsiveness (tolerance) is a key feature of the mucosal immune system, and deliberate vaccination or natural immunization by a mucosal route can effectively induce *immune suppression*." See, Czerkinsky at Summary (emphasis added). Moreover, the Examiner herself has admitted that Sigurdsson teaches that prion proteins are poor immunogens, stating in the Office Action dated December 28, 2007 at page 6, that, "prion proteins are regarded as poor immunogens [and] [v]accination with recombinant mouse prion protein delays the onset of disease but does not prevent the disease (Sigurdsson et al. Immunization delays onset of prion disease in mice. American Journal of Pathology, 2002, Vol. 161, No.1, pp. 13-17)."

Thus, based on the teaching of Czerkinsky and Sigurdsson's teaching that prion proteins are poor immunogens, one would not expect Sigurdsson's composition to induce a Th2-mediated immune response (i.e., overcome mucosal tolerance) against an endogenous prion protein (self protein) when administered mucosally, even if modified to contain a mucosally-suitable adjuvant, since his compositions did not even work when administered systemically with the very strong adjuvant CFA. In other words, Sigurdsson teaches away from modifying his composition to be suitable for mucosal administration, as required by Claim 1 and Claim 20, and their respective dependent claims.

Williamson and Prusiner each fail to disclose a composition containing a non-infectious, non-pathogenic prion protein, for the reasons discussed in detail above. In particular, Williamson and Prusiner only disclose a composition containing an *infectious* prion (PrP 27-30).

The secondary references do not cure the deficiency of Sigurdsson, Williamson or Prusiner, as, even if combined, they do not disclose or suggest any compositions which are recited in the present claims, i.e., compositions which (i) contain or express a *non-infectious, non-pathogenic* mammalian prion protein selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein, (ii) are suitable for *mucosal* administration, and (iii) when introduced to a

mammal's mucosal immune system, elicits a *primarily Th-2-type immune response against an endogenous prion protein* of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type CTL response.

Furthermore, as discussed in more detail below, none of the secondary references teach or suggest that Sigurdsson's CFA- and IFA-containing compositions could be administered mucosally without CFA or IFA, which are not suitable for mucosal administration, to successfully induce a Th2-mediated mucosal immune response, since Sigurdsson's compositions were hardly effective with CFA and IFA.

None of the secondary references teach that Williamson's or Prusiner's pathogenic prion PrP 27-30 should be substituted with a non-pathogenic, non-infectious prion protein, as required by the present claims. Thus, the skilled artisan could not have combined Sigurdsson, Williamson or Prusiner with any of the cited prior art references to arrive at the presently claimed composition.

Clements teaches CT-B as an adjuvant. Clements does not disclose or suggest any compositions containing or expressing a *non-infectious, non-pathogenic* antigen that, when introduced to a mammal's mucosal immune system, elicit a primarily Th-2-type immune response against an *endogenous* antigen of said mammal, as required by the present claims. In contrast to the present claims, Clements discloses eliciting immune responses against either *pathogenic* antigens (e.g., pathogenic strains of bacteria, col. 12, line 40 – col. 13, line 9) or against *non-endogenous* proteins (e.g., ovalbumin (OVA) (see col. 7, lines 9-39).

Kleanthous discloses the covalent attachment of CT-B to antigenic proteins. Kleanthous does not disclose or suggest any compositions containing or expressing a *non-infectious, non-pathogenic* antigen that, when introduced to a mammal's mucosal immune system, elicit a primarily Th-2-type immune response that is not associated with a primarily Th-1-type CTL response, as required by the present claims. In contrast to the present claims, Kleanthous only teaches eliciting a Th-l response through parenteral administration.

Lu and Chabalgoity teach effectiveness of Salmonella vectors in induction of mucosal immune responses. The present claims require the Shigella or Salmonella strain to be transformed with a vector capable of expressing a *non-infectious, non-pathogenic* mammalian prion protein, and not an antigen derived from an infectious pathogenic agent such as a bacteria or virus. In contrast to the present claims, Lu and Chabalgoity only disclose compositions expressing antigen derived from *infectious pathogenic* agents. See, e.g., Lu at col. 4, lines 47-49 (HIV antigen); Chabalgoity at page 466, 2nd col., ("live recombinant Salmonella that express heterologous antigens from other pathogens").

Furthermore, in contrast to the present claims, neither Lu nor Chabalgoity teaches or suggests any compositions that, when introduced to a mammal's mucosal immune system, elicit a primarily Th-2-type immune response that is not associated with a primarily Th-1-type CTL response. In fact, Lu discloses that the Salmonella vectors induce Th-1 responses (see Lu at col. 4, lines 53-64). Similarly, Chabalgoity discloses that the Salmonella typhimurium vectors expressing pathogenic antigens induced Th-1 responses, even when administered mucosally (see, Chabalgoity at page 466, 2nd col., last paragraph; emphasis added):

> ELISA analysis of the IgG subclasses of the antigen-specific antibody response, shows a clear polarization towards the IgG2 subclass for all antigens tested. Using the *salmonella* delivery system for studies conducted in mice, it has been shown that the immune responses elicited are *biased to a Th1 profile.*

Benkirane discloses that D-residues increase the antigenicity of antigenic peptides and lead to the generation of high levels of IgG3 antibodies. This reference does not disclose or suggest any of the composition properties (i)-(iii) recited in the present claims.

Grones discloses Shigella transformed with heterologous plasmids. This reference does not disclose any of the composition properties (i)-(iii) recited in the present claims.

Dunne discloses generation of transgenic bovine and cervid animals comprising a transgene encoding mutant PrP polypeptides generated by site-directed mutagenesis (see, e.g.,

¶ [0015]). Dunne expresses mutant PrP in *E. coli* pCR2.1 vectors and uses these vectors *in vitro* to generate transgenic embryos. This reference does not disclose any compositions comprising a wild-type PrP protein that are suitable for mucosal administration, and when introduced to a mammal's mucosal immune system, elicits a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type CTL response. Dunne's compositions were not designed to be immunogenic, but rather were designed to generate transgenic embryos.

Taken together, even if combined, the cited references do not disclose or suggest the compositions recited in the present claims.

In light of the foregoing arguments, the present claims are not obvious over the cited prior art. Withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In view of the above arguments and amendments, it is respectfully submitted that the present claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 641-2364. The Commissioner is hereby authorized to charge all requisite fees to our Deposit Account No. 06-1050.

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Respectfully submitted,

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